1. **Name of the Medicinal Product**
   Lemed-500 tablets
   (Levofloxacin tablets)

2. **Qualitative and Quantitative Composition**
   Qualitative Composition
   Each film coated tablet contains:
   Levofloxacin hemihydrate
   Equivalent to Levofloxacin .. 500 mg

Sr. No.	Ingredients	Standards
1	Levofloxacin hemihydrate equivalent to Levofloxacin	IH
2	Microcrystalline cellulose	BP
3	Ethylcellulose	BP
4	Isopropyl alcohol	BP
5	Croscarmellose sodium	BP
6	Magnesium stearate	BP
7	Hypromellose	BP
8	Propylene glycol	BP
9	Dichloromethane	BP
10	Titanium dioxide	BP
11	Purified talc	BP
12	Macrogols 6000	BP
13	Colour: Iron oxide red	IH

Quantitative Composition
Each film coated tablet contains:
Levofloxacin hemihydrate
Equivalent to Levofloxacin .. 500 mg

Sr. No.	Ingredients	Standards	Quantity/Batch of 1,00,000 tablets
1	Levofloxacin hemihydrate equivalent to Levofloxacin	IH	50.000 Kg
2	Microcrystalline cellulose	BP	29.300 Kg
3	Ethylcellulose	BP	1.700 Kg
4	Isopropyl alcohol	BP	42.500 Kg
5	Croscarmellose sodium	BP	2.000 Kg

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Sr. No.	Ingredients	Standards	Quantity/Batch of 1,00,000 tablets
6	Magnesium stearate	BP	2.000 Kg
7	Hypromellose	BP	1.500 Kg
8	Propylene glycol	BP	0.360 Kg
9	Dichloromethane	BP	24.500 Kg
10	Titanium dioxide	BP	0.200 Kg
11	Purified talc	BP	0.300 Kg
12	Macrogols 6000	BP	0.140 Kg
13	Colour: Iron oxide red	IH	230.000 g

3. Pharmaceutical Form

Film coated tablet

4. Clinical Particulars

4.1 Therapeutic Indications

Lemed-500 tablets are indicated in adults for the treatment of the following infections:

* Acute bacterial sinusitis
* Acute exacerbations of chronic bronchitis
* Community acquired pneumonia
* Complicated skin and soft tissue infections
* Pyelonephritis and complicated urinary tract infections
* Chronic bacterial prostatitis
* Uncomplicated cystitis
* Inhalation Anthrax: Post exposure prophylaxis and curative treatment

Lemed-500 tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Posology

The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.
Lemed-500 tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin; given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

The following dose recommendations can be given for Lemed-500 tablets:
Dosage in patients with normal renal functions (creatinine clearance > 50 ml/min)

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Indication	Daily dose regimen (according to severity)	Duration of the treatment (according to severity)
Acute bacterial sinusitis	500 mg once daily	10-14 days
Acute bacterial exacerbations of chromic bronchitis	500 mg once daily	7-10 days
Community acquired pneumonia	500 mg once or twice daily	7-14 days
Pyelonephritis	500 mg once daily	7-10 days
Uncomplicated cystitis	250 mg once daily	3 days
Complicated urinary tract infections	500 mg once daily	7-14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated skin and soft tissue infections	500 mg once or twice daily	7-14 days
Inhalation Anthrax	500 mg once daily	8 weeks

Special populations
Impaired renal function (creatinine clearance ≤ 50 ml/min)

Creatinine clearance	Dose regimen		
	250 mg/24 hours	500 mg/24 hours	500 mg/12 hours
	First dose: 250 mg	First dose: 500 mg	First dose: 500 mg
50-20 ml/min	Then: 125 mg/24 hours	Then: 250 mg/24 hours	Then: 250 mg/12 hours
19-10 ml/min	Then: 125 mg/48 hours	Then: 125 mg/24 hours	Then: 125 mg/12 hours
< 10 ml/min (including haemodialysis and CAPD)**	Then: 125 mg/48 hours	Then: 125 mg/24 hours	Then: 125 mg/12 hours

** No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired liver function

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No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

Elderly population
No adjustment of dose is required in the elderly, other than that imposed by consideration of renal function.

Paediatric population
Lemed-500 tablets are contraindicated in children and growing adolescents.

Method of administration

Lemed-500 tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dose. The tablets may be taken during meals or between meals. Lemed-500 tablets should be taken at least two hours before or after iron salts, zinc salts, magnesium or aluminium containing antacids or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents), and sucralfate administration, since reduction of absorption can occur.

4.3 Contraindications:

Lemed-500 tablets must not be used:

* in patients hypersensitive to levofloxacin or other quinolones
* in patients with epilepsy
* in patients with history of tendon disorders related to fluoroquinolone administration
* in children or growing adolescents
* during pregnancy
* in breast feeding women

4.4 Special warning and Precaution for use:

Methicillin-resistant *S. aureus* are very likely to posses co-resistance to fluoroquinolones, including levofloxacin. Therefore, levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA infections are considered inappropriate).

Levofloxacin may be used in the treatment of Acute Bacterial Sinusitis and Acute Exacerbation of Chronic Bronchitis when these infections have been adequately diagnosed.

Resistance to fluoroquinolones of *E. coli* - the most common pathogen involved in urinary tract infections - varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in E. coli to fluoroquinolones.
Inhalation Anthrax: Use in humans is based on in-vitro *Bacillus anthracis* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international concensus documents regarding the treatment of anthrax.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and has been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance. Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Clostridium difficile - associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of *Clostridium difficile* - associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treament with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concoitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

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Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin should be adjusted in patients with renal impairment.

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anphylactic shock), occasionally following the initial dose. Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Case of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin. Patients should be advisedto contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitization

Photosensitization has been reported with levofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or artificial UV rays (e.g. sunray lamp or solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitization.

Patients treated with vitamin K antagonists

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Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases, these have progressed to suicidal thoughts and self endangering behaviour, sometimes after only a single dose of levofloxacin. In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

QT interval prolongation

Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT intervals such as, for example:

* congenital long QT syndrome
* Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressents, macrolides, antipsychotics)
* uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
* cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

Peripheral neuropathy

Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Hepatobiliary disorders

Cases of hepatic necrosis up to life threatening hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases e.g. sepsis. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develops such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

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Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorder

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Super infection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If super infection occurs during therapy, appropriate measures should be taken.

Interference with laboratory test

In patients treated with levofloxacin, determination of opiates in urine may give false positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal product and other forms of interaction:

Effect of other medicinal products on levofloxacin

Iron salts, magnesium or aluminium containing antacid, didanosines

Levofloxacin absorption is significantly reduced when iron salts or Magnesium or aluminium containing antacids or didanosine (only didanosine formulation with aluminium or magnesium containing buffering agents) are administered concomitantly with Lemed-500 tablets. Concurrent adminsitration of fluroquinolones with multivitamns containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium or aluminium containing antacids, didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken 2 hours before or after Lemed-500 tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

The bioavailability of Lemed-500 tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin administration.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold. Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance. Caution should be exercised when levofloxacin is co-administered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renal impaired patients.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin was not affected to any clinically relevant extent when levofloxacin was adminstered together with the following drugs: Calcium carbonate, digoxin, glibenclamide, ranitidine.

<u>Effect of levofloxacin on other medicinal products</u>

Ciclosporin

The half life of ciclosporin was increased by 33% when co-administered with levofloxacin.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist

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(e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists.

Drugs known to prolong QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antodepressents, macrolides, antipsychotics).

Other relevant information
In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A3 inhibitor.

Other forms of interactions
Food
There is no clinically relevant interaction with food. Lemed-500 tablets may therefore be administered regardless of food intake.

4.6 Fertility, pregnancy and lactation:

Pregnancy
There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women.

Breast-feeding
The product is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to the experimental data suggests risk of damage by fluoroquinolones to the weight bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women.

Fertility
Levofloxacin caused no impairment of fertility or reproductive performance in rats.

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4.7 Effects on ability to drive and use machines:

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's abiity to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable Effects:

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.
Frequencies are defined using the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1000 - < 1/100)
Rare (≥ 1/10000 - < 1/1000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Not Known [a]
Infections and infestations		Fungal infection including *Candida* infection Pathogen resistance.		
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytppenia Neutropenia	Pancytopenia Agrabulocytosis Haemolyticanaemia
Immune system disorders			Angioedma Hypersensitivity	Anaphylactic shock[a] Anaphylactoid shock[a]
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients	Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reaction (with e.g. hallucinations, paranoia) Depression Agitation	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt

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System Organ Class	Common	Uncommon	Rare	Not Known [a]
			Abnormal dreams Nightmares	
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsions Parasethesia	Peripheral sensory neuropathy Peripheral sensory motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Synocope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision	Transient vision loss
Ear and labyrinth		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia Palpitation	Verticular tachycardia which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation) Electrocardiogram QT prolonged
Vascular disorders	Applies to I.V. form only Phlebitis		Hypotension	
Respiratory, thoracic and		Dyspnoea		Bronchospasm Pneumonities

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System Organ Class	Common	Uncommon	Rare	Not Known [a]
medistinal disorders				allergic
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, CGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily with severe underlying diseases Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash, Pruritus, Urticaria Hyperhidrosis		Toxic epifermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosentivity reactions Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders including tendinitis (e.g. Achilles tendon) Muscle weakness which may be of special importance in patients with myasthenia gravis	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) Ligament rupture Muscle rupture Athritis
Renal and urinary		Blood creatinine	Renal failure acute	

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System Organ Class	Common	Uncommon	Rare	Not Known [a]
disorder		increased	(e.g. due to interstitial nephritis)	
General disorders and administration site conditions	Applies to I.V. form only: Infusion site reaction (pain, reddening)	Asthenia	Pyrexia	Pain (including pain in back, chest and extremities)

[a] Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose
[b] Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolones administration include: Attacks of prophyria in patients with porphyria

4.9 Overdose:

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses. The most important signs to be expected following acute overdose of levofloxacin tablets are central nervous symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions. CNS effects include confusional state; convilsion, hallucination and tremor have been observed in post marketing experience.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body.

No specific antidote exists.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

ATC code: J01MA12

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Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enantiomer of the racemic drug substance ofloxacin.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to levofloxacin. Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 1 mg/L	> 2 mg/L
Pseudomonas spp.	≤ 1 mg/L	> 2 mg/L
Acinetobacter spp.	≤ 1 mg/L	> 2 mg/L
Staphylococcus spp.	≤ 1 mg/L	> 2 mg/L
S. pneumonia[1]	≤ 2 mg/L	> 2 mg/L
Steptococcus A, B, C, G	≤ 1 mg/L	> 2 mg/L

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Pathogen	Susceptible	Resistant
H. influenzae[2,3]	≤ 1 mg/L	> 1 mg/L
M. catarrhalis[3]	≤ 1 mg/L	> 1 mg/L
Non-species related breakpoints[4]	≤ 1 mg/L	> 2 mg/L

[1]The breakpoints for levofloxacin relate to high dose therapy.
[2]Low level fluoroquinolone resistance may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with *H. influenza*.
[3]Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
[4]Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible microorganisms

Aerobic gram positive bacteria
* *Bacillus anthracis*
**Staphycoccus aureus methicillin susceptible*
**Staphylococcus saprophyticus*
**Stretococci, groups C and G*
**Streptococcus agalactiae*
**Streptococcus pneumoniae*
**Streptococcus pyogenes*

Aerobic gram negative bacteria
**Eikenella corrodens*

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**Haemophilus inflenzae*
**Haemophilus para-inflenzae*
**Kebsiella oxytoca*
**Moraxella catarrhalis*
**Pasteurella multocida*
**Proteus vulgaris*
**Providencia rettgeri*

Anaerobic bacteria
**Peptostrptococcus*

Other
**Chlamydophila pneunomia*
**Chlamydophila psittaci*
**Chlamydia trachomatis*
**Legionella pneumophila*
**Mycoplasma pneumoniae*
**Mycoplasma hominis*
**Ureaplasma urealyticum*

Species for which acquired resistance may be a problem

Aerobic gram positive bacteria
**Enterococcus faecalis*
**Staphylococcus aureus* methicillin-resistant
*Coagulase negative *Staphylococcus spp.*

Aerobic gram negative bacteria
**Acinetobacter baumanni*
**Citrobacter freundii*
**Enterobacter aerogenes*
**Enterobacter cloacae*
**Escherichia coli*
**Klebsiella pheumoniae*
**Morganella morganii*
**Proteus mirablis*
**Providencia stuartii*

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Pseudomonas aeruginosa
Serratia marcescens

Anaerobic bacteria
Bacteroides fragilis

Inherently resistant strains

Aerobic gram positive bacteria
Enterococcus faecium
*Methicillin-resistant *Staphylococcus aureus* is very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

5.2 Pharmacokinetic Properties

Absorption
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 hours. The absolute bioavailability is 99-100%.
Food has little effect on the absorption of levofloxacin.
Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dose regimen.

Distribution
Approximately 30-40% of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 L after single and repeated doses indicating widespread distribution into body tissues.

Penetration into tissues and body fluids
Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebrospinal fluid.

Biotransformation
Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

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Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ($t_{½}$: 6-8 hours). Excretion is primarily by the renal route (> 85% of the administered dose).
The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/- 29.2 ml/min.
There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that oral and intravenous routes are interchangeable.
Linearity: Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

Special populations
Subjects with renal insufficiency
The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function, renal elimination and clearance are decreased, and elimination half lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose.

Cl_{cr} (ml/min)	< 20	20-49	50-80
Cl_R (ml/min)	13	26	57
$t_{½}$ (h)	35	27	9

Elderly subjects
There are no significant differences in levofloxacin kinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences
Separate analysis for male and female subjects showed a small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Pre-clinical Safety Data:
Non-clinical data reveal no special hazard based on conventional studies of single dose toxicity, repeated dose toxicity, carinogenic potential and toxicity to reproduction and development.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on foetuses was delayed maturation as a result of maternal toxicity. Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster cells in vitro. These effects can be

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attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DHA synthesis, dominant lethal tests) did not showany genotoxic potential).

Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenicity study.
In common with other flouroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose BP
Ethylcellulose BP
Isopropyl alcohol BP
Croscarmellose sodium BP
Magnesium stearate BP
Hypromellose BP
Propylene glycol BP
Dichloromethane BP
Titanium dioxide BP
Purified talc BP
Macrogols 6000 BP
Colour: Iron oxide red IH

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precaution for storage

Store below 30°C, protected from light and moisture.

6.5 Nature and contents of container (Packaging)

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10 tablets are packed in Alu-Alu strip. Such 1 strip is packed in a printed carton along with pack insert. 10 such cartons are packed in an outer carton.

6.6 Special precautions for disposal and other handling
No special requirements.

7. **Marketing Authorization Holder and Manufacturing Site Address**
Aglowmed Limited
Office:
702-A, Poonam Chambers, Worli,
Mumbai-400 018, India.
Email: ibd@aglowmed.com

Manufacturing Facility:
50/51, Raipur, Bhagwanpur, Roorkee,
Dist. Haridwar, Uttarakhand, 247 661

8. **Marketing Authorization Number**
Not applicable

9. **Date of First Authorization/ Renewal of Authorization**
Not applicable

10. **Date of Revision Text**
Not applicable

AGLOWMED LIMITED TECHNICAL DEPARTMENT INDIA